PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 9/52 — A1

(11) International Publication Number: WO 98/52547

(43) International Publication Date: 26 November 1998 (26.11.98)

(21) International Application Number: PCT/GB98/01513

(22) International Filing Date: 22 May 1998 (22.05.98)

(30) Priority Data:
9710699.1 24 May 1997 (24.05.97) GB

(71) Applicant *(for all designated States except US)*: DANBIOSYST UK LIMITED [GB/GB]; Albert Einstein Centre, Highfields Science Park, Nottingham NG7 2TN (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: ILLUM, Lisbeth [DK/GB]; 19 Cavendish Crescent North, The Park, Nottingham NG7 1BA (GB). PING, He [CN/CA]; University du Quebec à Montreal, Laboratoire d'Enzymologie Appliquee, Dept. Chimie–Biochimie, Succursale Centre–Ville, Case postale 8888, Montreal, Quebec H3C 3P8 (CA).

(74) Agent: BASSETT, Richard; Eric Potter Clarkson, Park View House, 58 The Ropewalk, Nottingham NG1 5DD (GB).

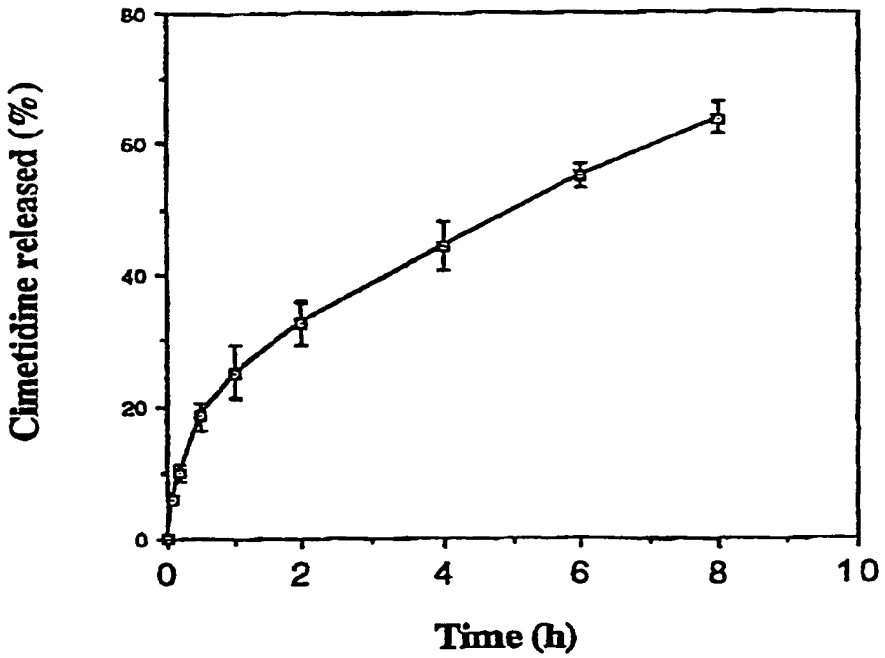
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: GASTRORETENTIVE CONTROLLED RELEASE MICROSPHERES FOR IMPROVED DRUG DELIVERY

(57) Abstract

There is provided a drug delivery composition for the controlled release of an active agent in the stomach environment over a prolonged period of time which comprises a microsphere comprising an active ingredient in the inner core of the microsphere and (i) a rate controlling layer of a water insoluble polymer and (ii) an outer layer of a bioadhesive agent in the form of a cationic polymer.



FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

GASTRORETENTIVE CONTROLLED RELEASE MICROSPHERES FOR IMPROVED DRUG DELIVERY

Field of the Invention

This invention relates to a novel method for retaining pharmaceutical agents in the stomach of a mammal, in order to provide local treatment of diseases of the stomach, or to improve the intestinal absorption of drugs which have a limited absorption capacity in the small intestine of such a mammal.

Background

The preferred route for the administration of most drugs is *via* the gastrointestinal tract. Most drugs are well absorbed from throughout the entire intestinal tract, but some compounds, usually those which are polar in nature, are poorly absorbed from the large intestine. For such drugs, the main area from which absorption occurs is the small intestine. Some drugs may exploit a natural pathway, such as receptor-mediated transport, active transport or other specific transport mechanisms, and are known to have so-called "absorption windows" in the small intestine. The term "absorption windows" describes the fact that a drug will be absorbed from a limited region of the intestine rather than the whole of the small and large intestines. The "window" could represent the duodenum, the jejunum or the ileum or parts thereof. Examples of such drugs include methyldopa and captopril. It would be advantageous to hold these drugs, which may display less than ideal absorption behaviour from the small intestine, in the stomach above their main absorption site for extended time periods, for example by way of a gastroretentive drug formulation.

A gastroretentive system would also be of value in the administration of a drug which is intended to produce a local effect in the stomach. A good example of this type of therapy is provided by way of the well known use of antibiotics in the local treatment of *Helicobacter pylori* (*H. pylori*). Furthermore, the use of antimicrobial substances for the treatment of *Campylobacter pylori* (with the additional treatment with other substances such as H_2-receptor blockers) is suggested in an article by Hirsche and Pletschette (1989) (*Campylobacter pylori and Gastroduodenal Ulcers* (Rathbone and Heatley, eds.), Blackwell (1989) p. 217). More particularly, these authors also suggest that, if retention in the stomach could be achieved, drugs which demonstrate topical activity could be readily administered orally for local treatment.

Various methods have been proposed in the prior art to achieve gastroretention, including dosage forms which display extended residence in the stomach due to their density or size, or through the use of mechanisms based on a putative bioadhesion concept.

The topic of gastroretentive dosage forms has been well reviewed by Moes (*Crit. Rev. Ther. Drug Carrier Syst.*, **10**, 143 (1993)) and Deshpande *et al* (*Drug Devel. Ind. Pharm.*, **22**, 531 (1996)). Proposed methods described in these review articles for prolonging the gastric residence time of drug delivery systems include agents such as fatty acids, pharmacological agents which delay the passage of material from the stomach to the small intestine, and devices such as unfolding polymer sheets and balloon hydrogels (Park, K. and Park, H., *Proc. Int. Symp. Control. Rel. Bioact. Mater.*, **14**, 41 (1987) and Cargill R., Caldwell, I.J., Engle, K., Fix, J.A., Porter, PA., and Gardner, C.R., *Pharm. Res.*, 5. 533, 1988).

While the concept of using large single unit dosage forms for gastric retention is attractive at first sight, potential problems, including blockage of the oesophagus or small intestine in certain patient groups, are known to be associated.

A further way to retain a drug delivery system in the stomach for an extended time period is to administer a non-disintegrating tablet or capsule, of a size greater than about 7 mm, and less than 20 mm, together with a large meal. The natural processes of gastric motility ensure that a delivery system of this size does not normally exit from the stomach until the stomach is empty of food. Thereafter the delivery system is cleared into the intestine through the action of a physiological process known as the migrating myoelectric complex (Phase III activity). However, in many instances, where drug absorption is affected by food, it would be advantageous to dose therapeutic agents to an empty, fasted stomach.

In the case of local treatment of gastric disorders, it would also be beneficial to achieve close adherence of a drug delivery system to the mucosal surface of the stomach, once the stomach has been emptied of liquid/food. Previous attempts to achieve this effect have not been successful, and no beneficial increase in residence time in man has been reported. By "beneficial increase in residence time" in this context, we mean that the residence time in the stomach for patients in the fasted state is at least three times greater than that for a control solution formulation.

The use of bioadhesive polymers as gastroretentive materials has been well reviewed in the pharmaceutical literature and is the subject of patent applications (see, for example, Ch'ng, H.S., Park, H., Kelly, P., and Robinson, J.R., *J. Pharm. Sci.*, 74, 399 (1985); Longer, M.A., Ch'ng,

H.S., and Robinson, J.R., *J. Pharm. Sci.*, 74, 406 (1985); and Gurney and Junginger (Eds.) *Bioadhesion Possibilities and Future Trends*, Wissenschafliche Verlaggeschelchaft (1990)).

Tablets and pellets with increased gastric retention and bioadhesive properties have been described in international patent application WO 94/00112. The specific use of microadherent formulations in the treatment of gastric disorders (including *H. pylori*) has been described in international patent application WO 92/18143. Natural gums, plant extracts, sucralfate, acrylic acid or methacrylic acid derivatives are suggested as means to give sustained release and/or prolonged retention in the stomach.

Controlled release mucoadhesive microgranules for the oral administration of furosemide are described in US patent No. 5,571,533. The granules are made from lipophilic excipients and are coated with mucoadhesive anionic polymers selected from the group: carbomer, polycarbophil, hydrodroxypropyl methyl cellulose, hydroxypropyl cellulose or admixtures thereof.

Moes (1993) (see reference above) reports that the use of bioadhesive polymers to modify gastrointestinal transit has been abandoned since such mucoadhesive polymers are not able to control or slow down significantly the gastrointestinal transit of solid delivery systems, such as pellets and tablets.

Pellets and other single units with a high density have also been investigated for gastroretention in Bechgaard, H. and Ladefoged, K., *J. Pharm. Pharmacol.*, 30, 690 (1978) and Clarke, G.M. *Gastrointestinal*

Transit of Spherical Granules of Differing Size and Density, PhD Thesis (1989), University of London), but the approach has not led to significant advantage in man unless the specific gravity is greater than 2.0. The skilled person will appreciate that such a high density presents a considerable disadvantage in a conventional pharmaceutical product from the standpoint of processing and weight.

Low density (floating systems) in the form of pellets and tablets have also been reported (Babu *et al*, *Pharmazie*, **45**, 268 (1990); Mazer *et al*, *J. Pharm. Sci.* 77, 647 (1988)). Whilst some small benefits can be demonstrated, such systems in their own right do not appear to provide extended periods of residence in the stomach. However, they do offer some protection against early and random gastric emptying, though, in order to do this, need to be administered immediately after a meal.

Floating minicapsules, having a size 0.1 to 2 mm, containing sodium bicarbonate, and which are coated by conventional water soluble film coating agents are described in US patent No. 4,106,120. Similar floating granules based on gas generation have been described in US patent No. 4,844,905. Floating capsules have also been described in US patent No. 5,198,229. Atyabi *et al*, (*J. Control. Rel.*, **42**, 105 (1996)) have described ion exchange systems containing bicarbonate that release CO_2 on contact with hydrochloric acid in the stomach, which gas is then trapped within a semi-permeable membrane surrounding the beads. This causes the particles to float. A suitable coating agent is disclosed as being Eudragit RS. The particles may then be given with food, though testing the formulation in question under the rigorous conditions of a fasted stomach is not described in the document in question. Moreover, no drug was incorporated into the particles to provide a slow release.

Burton *et al* (*J. Pharm. Pharmac.*, 47, 901 (1995)) studied gastroretention of an ion-exchange resin in the form of negatively charged fine particles in comparison with an aqueous solution in man. They found that the first 60 to 70% of the resin cleared at the same rate as an aqueous phase but the remaining 30 to 40% of the resin was retained for an extended period. All subjects were dosed after an overnight fast. Neither drug loaded microspheres nor gastroretentive systems with controlled release properties are mentioned or suggested.

European patent application EP 635 261 describes coated microparticles with improved drug absorption which consist of dehydrated microparticles comprising a nucleus of a gellable hydrocolloid onto which is deposited a film of cationic polysaccharide. The microparticles described in this document promote the absorption of drugs from the intestine. Gastroretention is not mentioned (on the contrary, it is suggested that the microparticles may be contained in an enterically coated gelatin capsule to protect the particles until they enter the duodenum). Incorporated within the matrix of the microparticles of EP 635 261 is a pharmacologically-useful drug. The hydrocolloids are preferably agar, pectin, xanthan gum, guar gum, locust bean gum, hyaluronic acid, casein and water soluble salts of alginic acid. The procedure for obtaining the microspheres is characterised by a multi-step process in which a solution of the gellable hydrocolloid is added to a medium in which gelling of the hydrocolloid takes place (eg calcium chloride). The microparticles so formed are separated and suspended in a concentrated solution of the drug from which the drug diffuses into the microparticles. The microparticles are then separated and suspended in a solution of cationic polysaccharide (such as diethylaminodextran) to effect deposition of the polysaccharide onto the

surface of the spheres. After this, the covered spheres are separated, washed and dried. No indication is given as to how the drug is retained in the particle during these various processing stages. The use of a rate controlling membrane as part of the composition of the microparticle is not mentioned. Moreover, no mention is made of the preparation of microparticles by spray drying.

Chitosan microspheres and microcapsules have been described previously as drug carrier systems. A review has been published by Yao *et al* (*J.M.S. - Rev. Macromol. Chem. Phy.*, **C35**, 155 (1995)). In order to make such systems, chitosan is cross-linked with an agent such as glutaraldehyde. Chitosan microcapsules, produced *via* a complex coacervation process, are also known. Alginate is a suitable negatively charged agent which may interact with positively charged chitosan (see for example, Polk *et al*, *J. Pharm. Sci.* **83**, 178 (1994)). Sustained release and floating granules based on chitosan have been described by Miyazaki *et al*, *Chem. Pharm. Bull.*, **36**, 4033 (1988) and Inouye *et al*, *Drug Des. Deliv.*, 4, 55, 1989. However, the particles mentioned in these documents are large in size and do not contain a release rate modifying polymer.

Chitosan compositions for controlled and prolonged release of macromolecules have been described in US patent No. 4,895,724. A porous matrix of chitosan is described, in which the macromolecule is dispersed. It is stated that the chitosan may be crosslinked by various agents to include glutaraldehyde, glyoxal, epichlorohydrin and succinaldehyde. The use of microspheres for bioadhesion or gastroretention is not suggested.

Chitosan microspheres have been described by others, for use in oral delivery, (Ohya *et al*, *J. Microencaps.*, **10**, 1 (1993); JP 5339149, EP 486 959, EP 392 487). However, such particles have not been prepared with a view to providing a controlled release effect.

In a recent international patent application (WO 93/21906) a range of bioadhesive polymers in the form of, or as coatings on, microcapsules containing drugs is described. Chitosan is described as performing poorly in bioadhesive tests. Moreover, the method of preparation of the chitosan microparticles may have rendered them negatively charged.

Thus, in summary, it would be of benefit to provide a system for delivering drug to the stomach which possessed the following attributes:

- a significant retention time in the fasted stomach of mammalian (e.g. human) subjects
- a high loading of water soluble and lipid soluble drugs
- a controlled release of such drugs over a period of time that is relevant to the clinical need (ie delivery of drug to the stomach, and/or enhanced drug uptake from an absorption window in the small intestine).

Other desirable attributes include:

- the preparation of such a formulation using established pharmaceutical processing methods
- the use of materials in the preparation of such a formulation that are approved for use in foods or pharmaceuticals or of like regulatory status.

Description of the invention

We have found, surprisingly, that microspheres comprising an inner core (optionally including a gelled hydrocolloid) containing a therapeutic agent (ie active ingredient or drug), a rate controlling membrane of water insoluble polymer (such as ethylcellulose) and an outer layer of a bioadhesive cationic polymer, which polymer may comprise a cationic polysaccharide, a cationic protein and/or a synthetic cationic polymer, may provide the necessary performance criteria, indicated above.

According to a first aspect of the invention, there is provided a drug delivery composition for the controlled release of an active ingredient in the stomach environment over a prolonged period of time which comprises a microsphere, which microsphere comprises an active ingredient in its inner core, and (i) a rate controlling layer of a water insoluble polymer and (ii) an outer layer of a bioadhesive agent in the form of a cationic polymer (hereinafter referred to as "the compositions of the invention").

Typically, the compositions of the invention are in the form of a plurality of microspheres that, upon administration to a mammal along with a suitable fluid (e.g. water), float initially on the stomach contents, and have a surface that provides a beneficial interaction between the particles and the mucus lining of the stomach, or with the wall of the stomach itself, when the stomach is emptied of liquid/food. The microsphere inner cores, which contain the drug in a sustained release system, are coated with a cationic polymer. The rate controlling layer can be either part of the inner core of the microsphere containing drug or present as a separate layer. Drug may be dispersed uniformly (homogeneously) or non-uniformly (heterogeneously) throughout the inner core. The compositions of the

invention may provide release of drug in the stomach environment (ie the gastric area) of the gastrointestinal tract over a prolonged period of time (e.g. at least twice as long as the stomach takes to empty itself of water (under normal conditions)).

For the purpose of this invention, by "microspheres", we include microparticles, which are substantially spherical and of "micron" size and microcapsules (which are microspheres or microparticles where the drug is encapsulated rather than dispersed homogeneously in the matrix). By "substantially spherical" we mean microparticles with a good sphericity (e.g. more than 80% of the particles have a longest measurable diameter which is less than or equal to two times greater in length than the shortest measurable diameter, as determined by light microscopy).

The microspheres may have a size in the range 0.5 to 1000 μm, more preferably in the range 1 to 700 μm and most preferably 5 to 500 μm, (mean volume diameter (MVD)) as measured using a laser diffraction method. We have found that the above size ranges give good retention in the stomach. Larger particles such as pellets and granules of a size greater than 1000 μm (eg 1000 to 2000 μm) do not adhere well.

We have found that the compositions of the invention have a low density and initially float on the contents of the stomach following administration with a suitable dosing liquid. When the stomach is emptied of its contents, the particles adhere to, and coat, the stomach wall.

Cationic polymers which may be used as bioadhesive agents in the outer layer include synthetic cationic polymers and, particularly, cationic polysaccharides and cationic proteins. The material is chosen such that

the microspheres carry a net positive charge, greater than +0.5 mV, more preferably greater than +5.0 mV, and most preferably greater than +10 mV (as measured by the technique of microelectrophoresis) at pH 4 in 0.001M buffer (such as a phosphate buffer, McIlvanes buffer, HEPES buffer).

Chitosan in the form of a salt is a preferred choice for use as the cationic bioadhesive material. Chitosan is non-toxic and is present in the diet. It is a positively charged biopolymer at gastric pH. It is known that chitosan may interact with negatively charged sialic acid groups in mucin (Fiebrig *et al*, *Progress in Colloid and Polymers Sci.*, **94**, 66 (1994)).

Chitosan is prepared by the deacetylation of chitin. The degree of deacetylation of chitosan should be greater than 40%, preferably greater than 60% and most preferably greater than 80%. The chitosan should have a molecular weight of greater than 5,000 D, preferably greater than 10,000 D and most preferably greater than 50,000 D. Chitosan can be employed as a chitosan salt (eg the glutamate, lactate, chloride or acetate salt) or as a chitosan derivative such as N-trimethyl chitosan chloride.

Other suitable bioadhesive cationic polymers which may be used include acidic (high isoelectric point) gelatin, polygalactosamine, proteins (polyaminoacids) such as polylysine, polyornithine, polyquaternary compounds, prolamine, polyimine, diethylaminoethyldextran (DEAE), DEAE-imine, polyvinylpyridine, polythiodiethylaminomethylethylene (PTDAE), polyhistidine, DEAE-methacrylate, DEAE-acrylamide, poly-p-aminostyrene, polyoxethane, co-polymethacrylates (eg copolymers of HPMA, N-(2-hydroxypropyl)-methacrylamide), Eudragit® RL, Eudragit® RS, GAFQUAT (see US patent No. 3,910,862), polyamidoamines,

cationic starches, DEAE-dextran and DEAE-cellulose. The polycationic substances used in the invention have a molecular weight of more than 5,000 D, preferably at least 50,000 D.

Preferred water insoluble polymers for use in the a rate controlling layer include ethylcellulose and polymethylmethacrylate. By "water insoluble polymer", we mean a polymer with a solubility in distilled water at pH 7 of less than 1 mg/mL at room temperature. The rate controlling layer and the cationic polymer may or may not comprise the same material (e.g. polymethylmethacrylate).

When the drug employed in the composition according to the invention is a polar drug, the inner core of the microsphere may further comprise a gelled hydrocolloid (i.e. a hydrocolloid that gels during microsphere production to provide structure (a reticulating agent)) with the therapeutic agent. Suitable hydrocolloid substances which may be employed include gelatin, albumin and alginates, for example agar, pectin, xanthan gum, guar gum, locust bean gum, hyaluronic acid, casein and water soluble salts of alginic acid. Gelling hydrocolloids may be gelled *via* appropriate means known to those skilled in the art (e.g. cooling of aqueous solutions, interaction with metal ions etc.)

By "polar drug" we mean a compound with a partition coefficient between water and octanol at pH 7.4 of less than 500.

The compositions of the invention may be provided by way of processes that produce compositions which provide for entrapment of the drug and its slow release in the stomach (see above). Thus, the compositions of the invention may be prepared *via* a variety of techniques, such as

emulsification followed by solvent evaporation under vacuum, spray coating etc. However, we have also found that the compositions of the invention may be prepared conveniently by way of an emulsification process combined with spray drying.

For polar drugs (which includes water soluble drugs), a novel double emulsion procedure (water-in-oil-in-water; w/o/w) may be used. We have found, surprisingly, that this particular method may be used to prepare floating microspheres that are positively charged and have controlled release properties, and is especially suitable for water soluble drugs.

Oil is defined herein as any liquid with a solubility in water of less than 2 mL (oil) in 10 mL (water) (i.e. it is immiscible with water).

By "water soluble" drugs, we include drugs which have sufficient solubility (eg more than 1 mg/mL, preferably more than 10 mg/mL) in the internal water phase of a double (w/o/w) emulsion, to enable the formation of microspheres from a subsequent spray drying process having a drug loading which is sufficiently high (eg more than 10%) to permit administration of the compositions of the invention so produced in a conventional capsule formulation or similar oral dosing system, such as a cachet or sachet, the content of which may be administered for example by, for example, dispersing in water and drinking.

In the preparation of compositions of the invention comprising polar drugs *via* an emulsification process, the water insoluble polymer which is used in the rate controlling layer may be dissolved in the oil phase.

For non-polar drugs, an oil-in-water (o/w) emulsification process may be used. In each case, the emulsions may be subsequently spray dried. By "non-polar drugs" we include drugs which are sufficiently soluble (i.e. more than 1 mg/mL, preferably more than 10 mg/mL) in an organic solvent (which solvents include dichloromethane, chloroform, ethyl acetate etc.), such that it drug is able to dissolve in the selected organic phase of an oil-in-water emulsion system in a sufficient quantity to enable the formation of microspheres from a subsequent spray drying process having a drug loading which is sufficiently high (eg greater than 10%) to permit administration of the compositions of the invention so produced in a conventional single unit hard capsule (eg one made from gelatin or starch) or a similar oral dosing system such as a cachet or sachet which content is administered by, for example, dispersing in water and drinking.

In the preparation of compositions of the invention comprising non-polar drugs, the therapeutic agent can be dissolved in the same solvent (ie the oil phase) that is used for the rate controlling layer.

It will be appreciated by the skilled person that the drug may be dissolved in the internal phase of the emulsion which is used, or can be suspended therein (depending on its solubility in this phase).

In the case of both polar and non-polar drugs, the bioadhesive cationic polymer is provided in an aqueous phase, being either the aqueous phase of the oil-in-water emulsion, or the external aqueous phase of the water-in-oil-in-water emulsion. Emulsions systems may be prepared in accordance with techniques which are well known to those skilled in the art, such as those described hereinafter.

When the compositions of the invention are produced by way of the emulsion processes described above, appropriate concentrations for use in the compositions of the invention are that the gelling hydrocolloid (if used) concentration for the preparation of the internal phase of the double emulsion is from 0.1% to 30%, preferably from 0.5 to 20%. The rate controlling layer is provided at a concentration of 0.5% to 20% in a suitable organic solvent, preferably from 1% to 10%. The organic solvent is preferably dichloromethane. The bioadhesive cationic polymer concentration used for the preparation of the external phase of the double emulsion is from 0.05 to 10% w/w but preferably from 0.1 to 5% and most preferably from 0.2 to 2%. Drug concentration may be from 0.01 to 90% depending on the drug which is employed. The above percentages are expressed as the weight of the particular component in the appropriate phase of the emulsion in which it is provided.

Following the formation of an appropriate emulsion system, the compositions of the invention may conveniently be prepared by spray drying, under conditions which are well known to those skilled in art. For example, the preparation of simple chitosan microspheres by spray drying chitosan dissolved in dilute acetic acid has been described in the prior art by Sugaya (Jpn. Kokai Tokyo Koho, JP 6320302). We have found that spray drying is a process for the preparation of microparticles for use with pharmaceuticals which can be scaled up readily.

The emulsion formulation can then be formed into microspheres using a suitable spray drying apparatus. Suitable apparatus include that described hereinafter in the examples. Other suitable equipment which may be employed include the apparatus available from Buchi in Switzerland, Niro/Aeromatic-Fielder (Switzerland/USA), LabPlant (UK) and Yamamoto

(Japan). The operating conditions such as the flow rate of the solution into the spray dryer, the size of the nozzle, the inlet and outlet air temperature, the atomization pressure, and the flow rate of the drying air, can be adjusted in accordance with the appropriate manufacturer's guidelines in order to provide the required particle size and release properties for the resultant microspheres. Such optimisation conditions can be easily selected by the person skilled in the art of pharmaceutical formulation paying proper attention to known methods of experimental design.

According to a further aspect of the invention there is provided a process for the preparation of a composition of the invention which comprises the spray drying of an oil-in-water, or a water-in-oil-in-water, emulsion including the components of the composition.

An improved gastric retention can be achieved for the compositions of the invention by increasing the pH of the stomach above the normal fasting range (1.5 to 2.5). Thus, the sialic acid residues in the mucus will be largely in the ionised form and will interact strongly with the cationic polymer. Certain foods can also produce an increase in pH to above pH 5 that lasts for a period of 30 minutes or longer. Patients receiving H_2-antagonists, proton pump inhibitors or antacids represent a special case, in which an advantage is provided by virtue of the fact that the gastric pH will be raised to 4 by the effect of the drug. Raising pH in this way may be particularly useful in the treatment of *H. pylori* infection.

Thus, according to a further aspect of the invention, there is provided a kit of parts for use in the treatment of *H. pylori* infection, including a composition comprising an H_2-antagonist, a proton pump inhibitor or an

antacid and a composition of the invention including a drug suitable for the treatment of *H. pylori*.

The compositions of the invention may, where appropriate, be surface hardened by, for example, and where appropriate, partially cross-linking by glutaraldehyde, formaldehyde, benzydianone, benzoquinone, tripolyphosphate or other cross-linking agents known to persons skilled in the art, in order to provide an intact bioadhesive surface layer that does not dissolve rapidly in the stomach and thereby fail to provide a beneficial bioadhesive effect. The conditions for carrying out the cross-linking, such as the amount of cross-linking agent required, are determined by monitoring the zeta potential of the microparticles and adjusting the process conditions until the required zeta potential (as determined for example by the technique of particle microelectrophoresis in a buffer of low ionic strength (0.001M) at a pH of 4.0) is obtained. The compositions of the invention carry a net positive charge, which is believed to provide a beneficial effect by allowing interaction with the negatively charged sialic acid groups of mucin.

The compositions of the invention may be administered to a mammal in suitable dosage forms, in accordance with techniques, and *via* delivery devices, all of which are known to those skilled in the art, for example by way of a capsule, a powder or as a compressed tablet, administered by mouth, that dissolves in the stomach to release the bioadhesive particle. The compositions may be administered with a suitable dosing liquid (e.g. water).

Active ingredients which may be included in the compositions of the invention include those which are suitable for the local treatment of

disorders of the stomach as well as compounds that typically display limited absorption from the gastrointestinal tract due to a limited absorption from the small intestine. Active ingredients which are useful in the treatment of diseases affecting the stomach include those suitable for the treatment of *H. pylori* infection, as well as H_2-antagonists and proton pump inhibitors. The following list is intended to provide examples and is not intended to be exclusive: metronidazole, ampicillin, doxycycline, tetracycline, oxytetracycline, itraconazole, ranitidine, cimetidine, famotidine, nizatidine and omeprazole.

Drugs that display preferential absorption from the small intestines and may be used in the compositions of the invention can be found in all therapeutic categories. A non-exclusive list is as follows: levodopa, methyldopa, furosemide, carvedilol, atenolol, topiramate, hydrochlorothiazide, captopril and orlistat (and other drugs for the treatment of obesity).

Combinations of the abovementioned therapeutic agents/active ingredients may also be employed.

For the avoidance of doubt, the term "therapeutic agents" is intended herein to include agents which are suitable for use in the treatment, and in the prevention, of disease.

The compositions of the invention may be used to treat/prevent diseases/conditions in mammalian patients depending upon the therapeutic agent(s) which is/are employed. For the above, non-exhaustive, lists of drugs, diseases/conditions which may be mentioned include those against which the therapeutic agent(s) in question are known to be effective, and

include those specifically listed for the drugs in question in Martindale, "*The Extra Pharmacopoeia*", 31st Edition, Royal Pharmaceutical Society (1996).

The amount of therapeutic agent which may be employed in the compositions of the invention will depend upon the agent which is used, and the disease to be treated, but may be in the range 0.1 mg to 10 g. However, it will be clear to the skilled person that suitable doses of therapeutic agents can be readily determined non-inventively. For example, estimates of dosage can be made from known injectable products assuming that from 0.1 to 100% of the dose is absorbed. Suitable single unit doses may be in the range 100 μg to 1000 mg depending upon the therapeutic agent(s) which is/are employed and the route of administration. Suitable daily doses are in the range 100 μg to 5 g/day depending upon the therapeutic agent(s) which is/are employed.

The compositions of the invention may be dosed once, or more (eg three) times, daily depending on the condition to be treated.

The compositions may also contain other additives in the form of pharmaceutical excipients, such as preservatives (e.g. low concentrations of materials such as sodium metabisulphate), stabilisers, flavouring agents, absorption enhancers such as bulking agents (e.g. lactose, microcrystalline cellulose), glidants and lubricants, bile salts, phospholipids and enzymatic inhibitors.

Compositions of the invention have the advantage that they may possess a significant retention in the fasted stomach of mammalian (e.g. human) subjects, may be used to incorporate a high loading of water soluble and

lipid soluble drugs and may provide a controlled release of such drugs over a period of time that is relevant to the clinical need.

Furthermore, compositions of the invention have the advantage that they may be used to assist in the retention of pharmaceutical agents in the stomach of a mammal, in order to provide local treatment of diseases of the stomach, or to improve the intestinal absorption of drugs which have a limited absorption capacity in the small intestine of such a mammal, depending on the drug which is used.

Moreover, compositions of the invention also have the advantage that they may be prepared using established pharmaceutical processing methods and employ materials in that are approved for use in foods or pharmaceuticals or of like regulatory status.

According to a further aspect of the invention there is provided a method of treatment or prophylaxis of a disease which comprises administration of a composition of the invention including a therapeutic agent which is effective against said disease to a patient in need of such treatment.

The invention is illustrated, but in no way limited, by the following examples, in which Examples 1 to 4 aim to demonstrate that, when employing certain methods, some of which are described in the prior art, it is not possible to produce a microsphere with a suitable performance. The subsequent Examples (5 to 7) are illustrative of the instant invention where controlled release gastroretentive microspheres can be prepared using a novel emulsion-spray drying method (water in oil in water (w/o/w) and oil in water (o/w) emulsions). Example 8 demonstrates that

compositions of the invention display enhanced retention in the stomach of human subjects.

The examples refer to the figures, in which:

Figure 1 shows the release profile of cimetidine loaded microparticles prepared by w/o emulsion-spray drying method.

Figure 2 shows the release profile of nizatidine loaded microparticles prepared by o/w emulsion-spray drying method.

Figure 3 shows the release profile of cimetidine loaded microparticles prepared by w/o/w emulsion-spray drying method.

Figure 4 shows the release profile of famotidine loaded microparticles prepared by w/o/w emulsion-spray drying method.

Figure 5 shows a histogram illustrating gastric emptying of a formulation comprising disodium clondronate tetrahydrate loaded microspheres prepared by a w/o/w emulsion-spray drying method.

Example 1

Preparation of Non-Crosslinked Chitosan Microspheres

Chitosan hydrochloride salt (0.3 to 0.4 g; Seacure CL 210 obtained from Pronova, Norway) was weighed into a 50 mL beaker and 20 mL of water was added to dissolve the chitosan. The resulting solution was made up to a volume of 100 mL using water and used for the spray drying process. Co-current spray drying was performed using a SD-04 spray drier (Lab

Plant, England), with a standard 0.5 mm nozzle. The inlet temperature was controlled at 160°C. The spray flow rate was controlled at 6 mL/min. The compressed spray air flow (represented as the volume of the air input) was set at 10 L/min. The resultant particles had good sphericity as determined by light microscopy (Nikon Optiphot) 20 or 40X magnification and were of a mean size of 6 micron (mean volume diameter (MVD)) as measured using a laser diffraction method (Malvern Mastersizer Model MS 1002). The particles carried a positive zeta potential (surface charge) of +27 mV as determined in 0.001M acetate buffer at pH 4.0 using a Malvern Zetasizer mark IV. For this measurement 1 to 3 mg of microspheres were dispersed in the buffer system.

However, the microspheres prepared by this method were found to swell in water, dissolve quite rapidly in pH 2.0 buffer (the conditions of the stomach). Such microspheres would therefore have a short lifetime in the stomach and have no controlled release characteristics, and thus be unsuitable for controlled drug delivery and gastroretention.

Example 2

Preparation of Crosslinked Chitosan Microspheres, with no Rate-Controlling Layer, using Spray Drying

In order to produce stable chitosan microspheres that would not swell and dissolve, drug free microspheres were prepared by a spray drying process using formaldehyde and glutaraldehyde as cross-linking agents.

The process used was as described in Example 1, but prior to spray drying, a defined amount of an aqueous solution of formaldehyde or

glutaraldehyde was added to the chitosan solution. The chitosan concentration was 0.1%. The defined amounts of cross-linking agent were 0.5, 1.0, 2.0, 4.0, 8.0 mL of a 1% formaldehyde solution and 0.5, 1.0, 1.5, 2.0, 4.0, 8.0 and 16.0 mL of a 1% glutaraldehyde solution.

The microspheres so produced had good sphericity. The size of those produced using cross-linking using formaldehyde were in the range 1.75 to 3.2 μm (MVD), the zeta potential, as measured in 0.001M pH 4 acetate buffer ranged from +16 to +20 mV. The greater the quantity of cross-linking agent, the lower the positive zeta potential. Similarly for glutaraldehyde cross-linked systems, the size (MVD) ranged from 1.5 to 3.7 μm and the zeta potential from +21 to + 14.5 mV; as previously, the greater the quantity of cross-linking agent, the lower the positive potential. When 0.2% chitosan solution was used with the same quantities of glutaraldehyde, the particles still had good sphericity but were somewhat larger in size (range from 8.8 to 2.3 μm; MVD). The zeta potentials were similar to those obtained with 0.1% chitosan solution. These microspheres did not contain drug; similar microspheres are prepared below which include drugs.

Example 3

Preparation of Drug Loaded Microspheres using Spray Drying

Microspheres were prepared using a method similar to that in Example 2.

10 mg of cimetidine was added to 500 mL of 0.1% or 250 mL of 0.2% chitosan aqueous solution. A specific amount of 2% glutaraldehyde aqueous solution or 1% formaldehyde aqueous solution was added with

stirring using a magnetic stirrer. The spray drying was effected following the procedure as in Example 1.

The properties of the microspheres were as follows: The microspheres were found to be spherical in all cases. Drug loading was approximately 17% w/w. The size ranged from 2.0 to 7.9 μm (MVD) depending on the initial concentration of the chitosan used (0.1% or 0.2%) and the amount of cross-linking agent added (1 to 4 mL of 4% glutaraldehyde). The zeta potentials at pH 4.0 in 0.001M acetate buffer were in the narrow range of +15 to +17 mV. Similar results were obtained using formaldehyde as the cross-linking agent.

Drug loading was measured as follows: a defined amount of drug-loaded chitosan microspheres, accurately weighed, was placed in a 50 mL volumetric flask. The mixture was dispersed and diluted to volume with 0.1N sulphuric acid. The suspension was sonicated in an ultrasonic bath (Decon FS 100) for 10 minutes and held overnight at room temperature to allow the drug to fully dissolve from the microspheres. 5 mL of the suspension was filtered with a 0.2 μm syringe filter to remove particulate material and the absorbance was determined. The drug contents were measured spectrophotometrically.

In vitro release was determined as follows: an *in vitro* test was carried out using a dissolution apparatus (Copley-Erweka DT-6) with the dissolution paddle assembly (USP Apparatus 2 or BP Apparatus 11). Samples were suspended in 300 mL of pH 7.4 phosphate buffered saline at 37°C, at 50 rpm agitation rate. A specific amount of drug loaded microspheres, accurately weighed, was added into each vessel. 3 mL of the sample was drawn into a syringe at predetermined time intervals. The same amount of

the fresh dissolution medium was added to the system. The samples were filtered and the drug content measured spectrophotometrically. Pure unincorporated free drug was used as a control. The dissolution measurements showed that the release of the H_2-antagonist from the chitosan microspheres prepared by the spray drying method was extremely rapid. The majority of the drug was released in less than 15 minutes and the dissolution profile was essentially similar to the unincorporated drug.

Thus, while cross-linked chitosan microspheres of a small particle size and positive charge and with good drug loading could be prepared, the release of the incorporated drug was very rapid and the products prepared would be of no clinical value.

Example 4

Preparation of Controlled Release Microspheres using a Water-in-Oil Emulsification Process Followed by Spray Drying

The work described in the examples above clearly demonstrate that simple stabilised chitosan microspheres as described in the prior art are not suitable as gastroretentive systems that provide controlled release of an incorporated drug. In order to delay drug release, an alternative process was investigated using an emulsification process where ethylcellulose was employed as a drug retention agent. In addition the water soluble drug was first dissolved in gelatin so as to provide a reticulation agent to provide a physical structure to the inside of the spray dried microspheres so produced.

0.1 g of gelatin A and 0.1 g of drug (cimetidine or famotidine) were weighed into a 16 mL test tube. 5 mL of distilled water was added. A clear solution was obtained when the mixture was heated to 60°C.

0.4 g of the water insoluble polymer ethylcellulose (EC-Dow) was dissolved in 50 mL of dichloromethane in a 100 mL beaker. The aqueous solution containing the drug and gelatin was added dropwise into the oil phase under magnetic stirring. This system was then homogenized at 11,000 rpm for 2 minutes. The water-in-oil (w/o) emulsion formed was directly spray dried under the following conditions: Co-current spray drying was performed using a SD-04 spray drier (Lab Plant, England) with a standard 0.5 mm nozzle. The inlet temperature was controlled at 50°C. The spray flow rate was controlled at 8 mL/min.

Table 1

Characteristics of microparticles prepared by a w/o emulsion-spray drying method

Drug	Drug content (%)	Size (μm)	Zeta potential (mV; pH 7)*
Cimetidine	15.5	6.04	-4.0
Famotidine	12.8	10.09	-3.3

*Phosphate buffer 0.0001 M

The physico-chemical characteristics of the particles prepared by w/o emulsion-spray drying method are shown in Table 1. Poor sphericity was observed. The particle size was about 10 μm. Since a positively charged material, eg. chitosan, was not used in this example, the particles so prepared were negatively charged.

Drug release from the microparticles prepared by the w/o emulsion-spray drying method was carried out in a dissolution apparatus as previously described. The release profile of the cimetidine loaded microparticles prepared by w/o emulsion-spray drying method is shown in Figure 1. Cimetidine release from the particles was greatly retarded, compared with the drug loaded microspheres prepared by the conventional spray drying method with chitosan, as described in Example 1. The drug was released gradually over several hours.

The microparticles were seen to float on the surface of the dissolution medium. The addition of a wetting agent to the dissolution medium in the form of 0.05% Tween 80 gave rise to an increased release rate.

Example 5

Preparation of Controlled Release Microspheres by an Oil-in-Water (o/w) Emulsion/Spray Drying Method

In those situations where the drug is sufficiently soluble in the organic solvent it is possible to prepare a drug loaded microsphere using an oil in water emulsion. Here the oil phase which contains the drug and ethylcellulose (or other suitable controlled release polymers) is dispersed in the aqueous chitosan solution and then spray dried. This method can be exemplified using the H_2-antagonist nizatidine.

0.1 g nizatidine and 0.2 g ethylcellulose were dissolved in 5 mL of dichloromethane in a 16 mL test tube. It was added dropwise into 100 mL 0.4% chitosan aqueous solution under magnetic stirring. Homogenization was performed at 12,500 rpm for 1 minute and the mixture sonicated if

necessary. After the addition of 2 mL of 4% glutaraldehyde aqueous solution, the emulsion was spray dried. Co-current spray drying was performed using a SD-04 spray drier (Lab Plant, England) with a standard 0.5 mm nozzle. The inlet temperature was controlled at 13°C. The spray flow rate was controlled at 6 mL/min. The air flow rate was set at 10 L/min. The sphericity for the drug loaded microparticles was good. The particle size of the drug loaded microspheres was 7.7 μm (MVD). The zeta potential at pH 4.0 at an ionic strength of 0.001M was +9.0 mV. The drug loading was 8.4% w/w.

The release of drug was measured using the USP dissolution method as described in Example 3. The concentration of nizatidine was measured by an ultraviolet spectroscopic method at 313 nm according to the method of Wozniak (*Analytical Profiles of Drug Substances*, **19**, Ed. K. Florenz, Academic Press, San Diego, p. 397, 1990). A controlled release profile was obtained (Figure 2).

Example 6

Preparation of Floating Microspheres Prepared by a Novel w/o/w Emulsion Spray Drying Method

Chitosan microspheres prepared by a conventional-spray drying method as described in Example 3 had a good sphericity and were positively charged. However, the rate of release of H_2-antagonist from the microspheres was fast and accompanied by a "burst effect". Drug release from the microparticles prepared by a w/o emulsion-spray drying method as described in Example 4 was retarded, but the particles are not gastroretentive. In the following method, positively charged microspheres were prepared.

0.1 g of gelatin type A and 0.1 g of a water soluble drug (cimetidine or famotidine) were weighed into a 16 mL test tube. 5 mL of distilled water was added. A water phase consisting of a clear solution was obtained when the mixture was heated to 60°C. This is termed the internal phase. An oil phase consisted of 0.2 gram of ethyl cellulose (Dow), dissolved in 25 mL of dichloromethane in a 50 mL beaker. An external water phase was composed of 150 mL of 0.3% chitosan (MW 140-160 kD) aqueous solution in a 200 mL beaker.

The internal water phase was added dropwise into the oil phase under magnetic stirring. The system was then homogenized using a Silverson homogenizer (Silverson, Chesham, Bucks, UK) at 11,000 rpm for 2 minutes. Sonication was performed if necessary. This primary emulsion was then added dropwise into the external water phase under magnetic stirring. Further homogenizing was provided at 10,000 rpm for 2 minutes. 2 mL of 4% glutaraldehyde was used as a cross-linking agent before spray drying. Co-current spray drying was performed using a SD-04 spray drier (Lab Plant, England), with a standard 0.5 mm nozzle. The inlet temperature was controlled at 150°C. The spray flow rate was controlled at 6 mL/min. Drug free microspheres were prepared according to the same procedure, without addition of the drug.

The characteristics of the drug free microspheres prepared by w/o/w emulsion-spray drying method are listed in Table 2. The formation of the w/o/w double emulsion was confirmed using light microscopy (before spray drying) and the characteristics of the floating behaviour of the formed microspheres were also evaluated using a suitable dissolution medium (USP-simulated gastric fluid). Under scanning electron

microscopy, their particles were seen to be hollow when fractured, which demonstrates the low density and potential floating characteristics. The w/o/w emulsion formed was very good, as assessed by light microscopy, in that the "oil particles" were seen to contain water droplets. The size of the w/o/w emulsion droplets and harvested microspheres were dependent upon mixing rate and nozzle mounting position of the spray drying apparatus. A fast rate of mixing (or sonication) led to a smaller particle size. Larger microspheres were produced by counter-current spray drying. The emulsion particles formed were about 20-40 μm in diameter.

After the solvent of the emulsion was removed by evaporation, the size of the particles was reduced to about 10 to 15 μm. In order to prepare microspheres with a size of 10 μm, and with a floating character, a procedure was adopted where the mixing rate for both primary and secondary emulsion was set at 12,600 rpm for 1 minute followed by conventional co-current spray drying.

The characteristics of the drug-loaded microspheres so prepared are shown in Table 3. The particle size was similar to that for drug free microparticles. The particles were positively charged. The drug loading was high. The sphericity was acceptable.

An *in vitro* test was carried out using a dissolution apparatus as described hereinbefore. The dissolution paddle assembly (USP Apparatus 2 or BP Apparatus II) was used. However, the basket assembly (USP Apparatus 1 or BP Apparatus 1) was used. The microspheres were filled into hard gelatin capsules. Samples were weighed into the capsules individually and were released into 300 to 500 mL of pH 7.4 phosphate buffered saline or simulated gastric fluid, containing different amount of the surfactant

Tween 80 (used to evaluate the influence of the amount of the wetting agent on the rate of release). The temperature and agitation were set at 37°C and 50 rpm, respectively. 3 mL of the dissolution sample was drawn into a syringe at predetermined time intervals. The same amount of the fresh dissolution medium was supplied to the system. The samples were filtered with 0.2 μm syringe filters. The contents of the drug were measured spectrophotometrically.

Table 2

Characteristics of the drug free microspheres prepared by the w/o/w emulsion/spray drying method

Mixing rate for the emulsion		Size of w/o/w Emulsion (μm)	Size of Harvested Microspheres (μm)	Floating Character
Primary	Secondary			
12,600;1 min	12,600;1 min	<20	9.71	+
12,600:30 sec	12,600;30 sec	40-80	16.41	++
12,600:1 min*	12,600;30 sec	5-10	7.71	+
12,600;1 min	12,600;30 sec	20-40	20.93**	+

*Sonication for the primary emulsion

**Counter-current spray drying

+ good degree of floating ability

++ excellent degree of floating ability

Table 3

Characteristics of the drug loaded microspheres prepared by the w/o/w emulsion-spray drying method.

Drug Loaded	Drug Content (%)		Size	Zeta Potential
	Added	Found	(μm)	mV (pH 4)
Cimetidine	13.3	12.7	11.68	+13.4
Cimetidine	15.5	12.7	9.58	+13.0
Famotidine	13.2	13.1	14.44	+10.2
Famotidine	5.5	3.8	11.57	+11.0

The release of cimetidine and famotidine from floating chitosan microspheres was tested in the dissolution media, phosphate buffered saline (PBS) and simulated gastric fluid (SGF), in the presence of different amounts of the wetting agent, Tween 80. The results are shown in Figures 3 and 4. All microspheres had slow release characteristics, even in the presence of the wetting agent.

Example 7

Preparation of Floating Microspheres Prepared by a Novel w/o/w Emulsion Spray Drying Method without the Addition of a Cross-Linking Agent

4 g of chitosan glutamate (SeaCure G210, Pronova) was weighed into a 1 litre volumetric flask and dissolved in approx. 600 mL of deionised water. The solution was made up to 1 litre with water. 2.4 g of ethylcellulose (45 cps, Dow) was dissolved in 120 mL of dichloromethane. 0.6 g of gelatin A (175 bloom, Croda) was weighed into a 20 mL volumetric flask

and dissolved by adding approx. 15 mL deionised water and warming to approx. 50°C. The solution was made up to 600 mL with water. 12.6 g of disodium clodronate tetrahydrate was weighed into a beaker and dissolved by adding the 20 mL of gelatin solution. 600 mL of the chitosan solution was transferred into a 1 litre beaker and chilled in an ice bath for at least 5 minutes.

The gelatin/clodronate solution and the 120 mL of ethylcellulose solution were transferred into a 250 mL beaker. The mixture was emulsified for 1 minute using a Silverson homogeniser (model L4R) set at 10,000 rpm to produce a water-in-oil emulsion. The beaker was placed into an ice bath during emulsification to prevent the emulsion overheating.

The water-in-oil emulsion (gelatin/clodronate-in-ethylcellulose) was added to the 600 mL of chitosan solution and emulsified for 1 minute at 10,000 rpm using the Silverson mixer to produce a water-in-oil-in-water emulsion.

The water-in-oil-in-water emulsion was immediately spray-dried using a Lab Plant SD-05 equipment set an inlet temp. of 169°C, exhaust temp. of 79°C, air pressure of 1.9 bar and air flow of 22 units. The emulsion was pumped into the equipment via a Cole-Parmer peristaltic pump set at 11 mL/min. The total processing time was approx. 70 minutes.

A fine white powder was produced with a mean particle size in the range 5 - 10 μm as measured by light microscopy. The process yield was of the order 20-40%.

The clodronate content of the spray-dried powder was assayed using a GC-MS method.

The formulation contained 60% w/w anhydrous disodium clodronate.

The spray-dried powder was filled into size 0 hard gelatin capsules - 238 mg/capsule for administration to man.

The dissolution performance of the filled capsules was measured using EP/USP method 2. One capsule was placed into each dissolution vessel containing 900 mL of 0.01M HCl as the test medium. Each vessel was agitated by paddle set at 100 rpm. Samples of dissolution medium were withdrawn at regular intervals over a 4 hour period and assayed by GC-MS for clodronate content. At the end of testing, the capsule shells had dissolved and the spray-dried powder remained floating on top of the dissolution medium. Slow release of the clodronate was found where 25% of the drug was released in 150 minutes.

Example 8

The Measurement of Gastroretention in Human Subjects

The gastroretentive microsphere formulation described in Example 7 was evaluated in a group of 9 healthy fasted subjects aged between 50 and 70 years. The formulation was labelled with a gamma emitting radionuclide (indium^{111}) by the addition of a small amount of ion-exchange resin to the formulation. A marker for the gastric emptying of a simple liquid formulation in the form of a techetium-99m labelled diethylenetriaminepentaacetic acid (DTPA) solution was used as a control.

Concomitant administration of the microspheres (0.5 MBq) and solution (3 MBq) took place. The pellets (contained in a hard gelatin capsule) were given with the DTPA solution in 200 mL of water.

The subjects were placed in front of a gamma camera (GE-Maxi camera) and anterior and posterior images recorded at two energy levels to monitor both radionuclides. Images were recorded every 15 minutes until 6 hours after dosing. Two hours after dosing a drink of 200 mL of water was allowed. The recorded images were analysed by a standard method (geometric mean calculation) in order to obtain gastric emptying profiles for both the gastroretentive system and the control.

The data are shown in Figure 5 in histogram form.

A dramatic difference between the control solution and the gastroretentive microspheres was well demonstrated. The gastroretentive system took longer to empty from the fasted stomach than did the control solution at all time points chosen.

Claims

1. A drug delivery composition for the controlled release of an active ingredient in the stomach environment over a prolonged period of time which comprises a microsphere comprising an active ingredient in the inner core of the microsphere and (i) a rate controlling layer of a water insoluble polymer and (ii) an outer layer of a bioadhesive agent in the form of a cationic polymer.

2. A drug delivery composition as claimed in Claim 1, wherein the cationic polymer is a cationic polysaccharide, a cationic protein, or a synthetic cationic polymer.

3. A composition as claimed in Claim 1 or Claim 2 wherein the inner core contains a gelling hydrocolloid.

4. A composition as claimed in any one of the preceding claims wherein the water insoluble polymer is ethylcellulose.

5. A composition as claimed in any one of the preceding claims wherein the cationic bioadhesive agent is chitosan.

6. A composition as claimed in any one of Claims 1 to 4 wherein the cationic bioadhesive agent is diethylaminoethyldextran.

7. A composition as claimed in any one of Claims 3 to 6 wherein the gelling hydrocolloid is gelatin.

8. A composition as claimed in any one of the preceding claims obtainable by the spray drying of an oil-in-water or of a water-in-oil-in-water emulsion including the components of the composition.

9. A composition as claimed in any one of the preceding claims wherein the active ingredient is useful in the local treatment of a disease of the stomach.

10. A composition as claimed in any one of the Claims 1 to 8 wherein the active ingredient has a limited absorption capacity in the small intestine of a mammal.

11. A composition as claimed in any one of Claims 1 to 9 wherein the active ingredient is useful in the treatment of *Helicobacter pylori*.

12. A composition as claimed in any one of Claims 1 to 9 wherein the active ingredient is useful in the treatment of *Campylobacter pylori*.

13. A composition as claimed in any one of Claims 1 to 9 wherein the active ingredient is an a H_2-antagonist or a proton pump inhibitor.

14. A composition as claimed in any one of Claims 1 to 9 wherein the active ingredient is a bisphosphonate.

15. A pharmaceutical formulation in a form suitable for oral administration, which formulation comprises a composition according to any one of Claims 1 to 14 in a pharmaceutically acceptable dosage form.

16. The use of a composition according to any one of Claims 1 to 14, or a formulation according to Claim 15, as a means of delivery of therapeutic agents to the stomach.

17. The use of a composition according to any one of Claims 1 to 14, or a formulation according to Claim 15, in the gastroretention of an active ingredient.

18. A method for achieving gastroretention which comprises the administration a composition according to any one of Claims 1 to 14, or a formulation according to Claim 15, to a patient.

19. A method for the treatment or prophylaxis of a disease which comprises administration of a composition according to any one of Claims 1 to 14, or a formulation according to Claim 15, including an active ingredient which is effective against said disease, to a patient in need of such treatment or prophylaxis.

20. A method as claimed in Claim 19, wherein the disease in one of the stomach, and the active ingredient of the composition or formulation is useful in the local treatment of said disease.

21. A method for the improved the gastrointestinal absorption of drugs which have a limited absorption capacity in the small intestine, which comprises administration of a composition according to any one of Claims 1 to 14, or a formulation according to Claim 15, comprising such a drug to a patient.

22. The use of a composition according to any one of Claims 1 to 14 in the manufacture of a medicament for the treatment or prophylaxis of a disease which comprises administration of said composition, including a therapeutic agent which is effective against said disease, to a patient in need of such treatment or prophylaxis.

23. The use of a composition according to any one of Claims 1 to 14 in the manufacture of a medicament for use in a method of treatment according to any one of Claims 18 to 21.

24. A kit of parts for use in the treatment of *H. pylori* infection, including a composition comprising an H_2-antagonist, a proton pump inhibitor or an antacid, and a composition according to Claim 11.

25. A process for the preparation of a composition according to any one of Claims 1 to 14 which comprises the spray drying of an oil-in-water, or of a water-in-oil-in-water emulsion including the components of the composition.

Figure 1

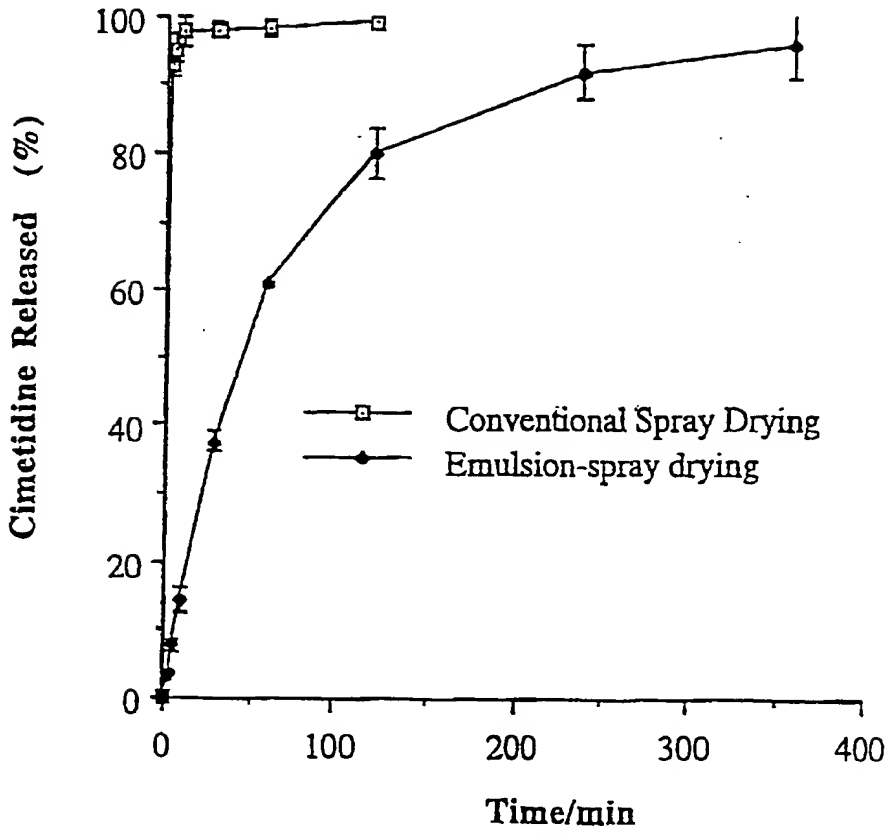

Cimetidine Released (%)
100
80
60
40
20
0
0
100
200
300
400
Time/min
Conventional Spray Drying
Emulsion-spray drying

Figure 2

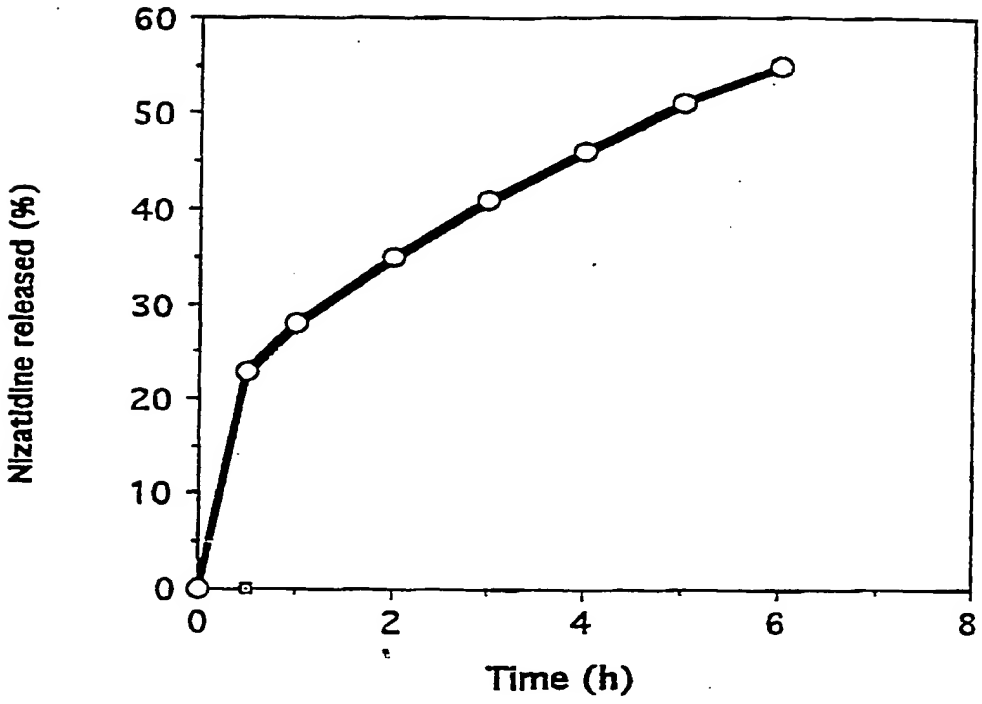


Figure 3

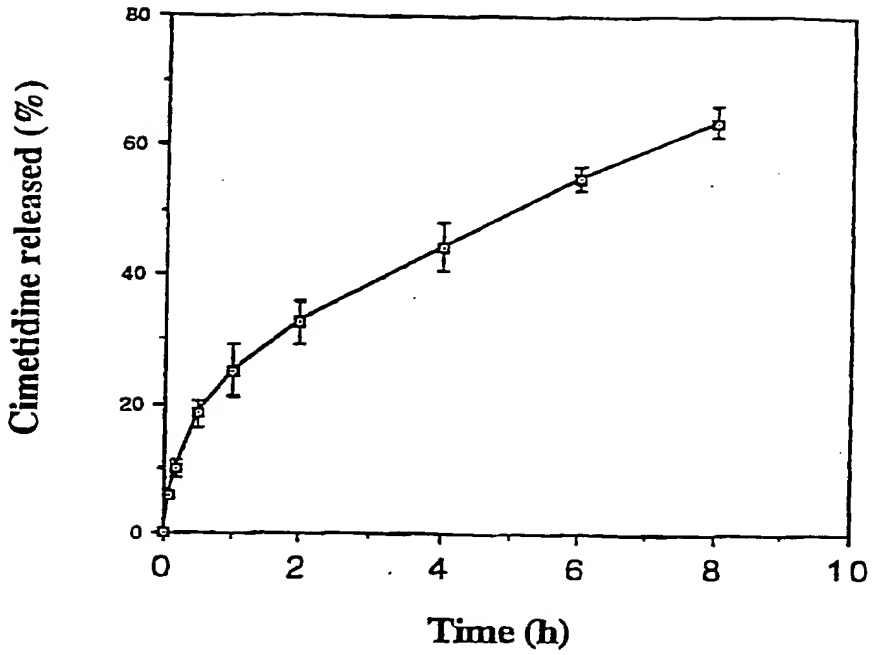


Figure 4

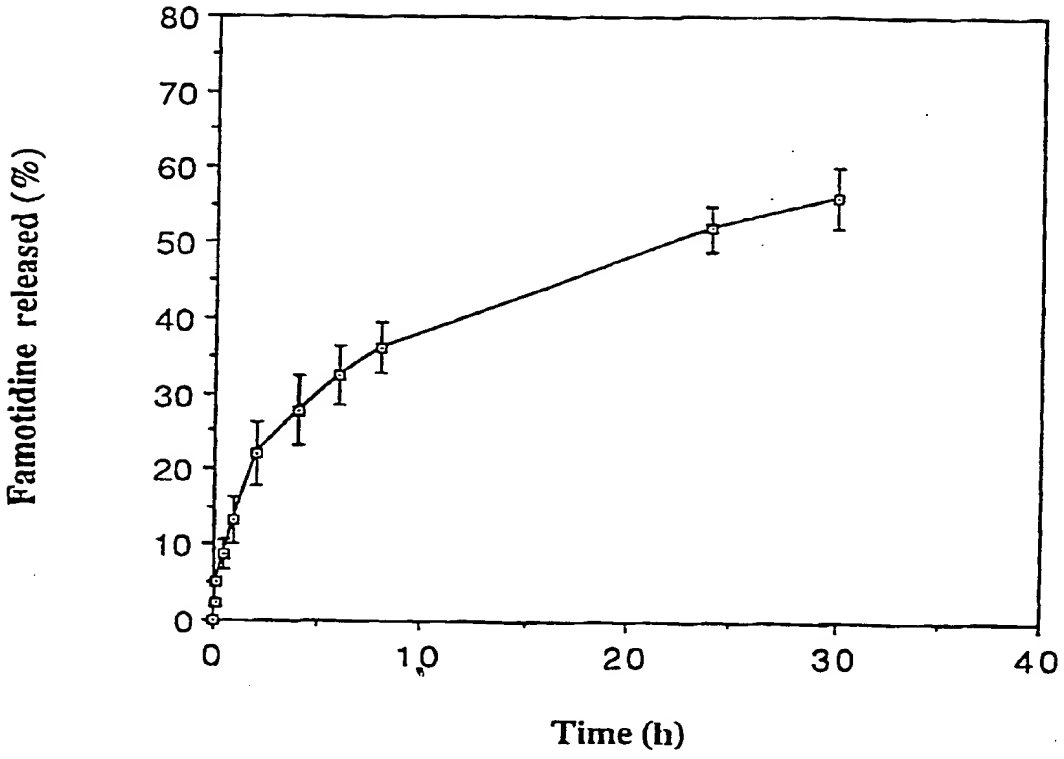


Figure 5


Gastroretentive system
Drink
Formulation remaining in stomach (% of original)
125
100
75
50
25
0
0
14
17
44
47
Time (min)

INTERNATIONAL SEARCH REPORT

Int. ational Application No
PCT/GB 98/01513

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/52

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 516 141 A (RECORDATI CHEM PHARM) 2 December 1992 see abstract see page 3, line 22-55 see page 5, line 40 see examples 3,5-7 see claims 1,4,5 --- -/--	1,16-18

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 September 1998	15/09/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	La Gaetana, R

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int. ational Application No
PCT/GB 98/01513

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94 00112 A (ASTRA AB) 6 January 1994 cited in the application see page 1, line 6-12 see page 3, line 18-22 see page 4, line 27-29 see page 5, line 17 - page 6, line 17 see example 4 see claims	1,2,4,5, 8,9, 11-13, 15-20, 22-24
A	EP 0 635 261 A (LIPOTEC SA) 25 January 1995 cited in the application see abstract see page 3, line 20-24 see examples see claims 1,5,6,9	1,2,6
A	WO 85 02092 A (BIO MIMETICS INC) 23 May 1985 see abstract see page 6, line 13 - page 8, line 7 see examples 4,5 see claims 1,4,5	1,3,7

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 98/01513

Box I Observations where certain claims wer found unsearchable (Continuation f item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 18-21
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee. this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte. ational Application No
PCT/GB 98/01513

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0516141 A	02-12-1992	IT 1250421 B	07-04-1995
		AT 141159 T	15-08-1996
		DE 69212710 D	19-09-1996
		DE 69212710 T	19-12-1996
		DK 516141 T	02-09-1996
		ES 2091363 T	01-11-1996
		GR 3020813 T	30-11-1996
		JP 7215843 A	15-08-1995
		US 5472704 A	05-12-1995
WO 9400112 A	06-01-1994	AU 4517893 A	24-01-1994
		SI 9300330 A	31-12-1993
EP 0635261 A	25-01-1995	ES 2068762 A	16-04-1995
		JP 7145044 A	06-06-1995
		US 5736161 A	07-04-1998
WO 8502092 A	23-05-1985	AT 151286 T	15-04-1997
		AU 565354 B	10-09-1987
		AU 3618484 A	03-06-1985
		DE 3485995 A	07-01-1993
		DE 3486448 D	15-05-1997
		DE 3486448 T	09-10-1997
		EP 0163696 A	11-12-1985
		EP 0501523 A	02-09-1992
		HK 121497 A	12-09-1997
		JP 8030004 B	27-03-1996
		JP 61500612 T	03-04-1986
		US 4983392 A	08-01-1991
		US 5225196 A	06-07-1993
		US 4615697 A	07-10-1986
		US 4795436 A	03-01-1989